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Reductive Cyclization and Petasis-like Reaction for the Synthesis of Functionalized γ -Lactams

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and Thomas E. Nielsen^{*,[a,c]}

Abstract: An efficient reductive cyclization strategy was employed for the synthesis of *N*-substituted β,γ -dihydroxy- γ -lactams. A subsequent Petasis-like reaction (PLR) through nucleophilic additions of boronic acids to intermediate *N*-acyliminium ions produced substituted γ -lactams. Overall, the application of this protocol provides β,γ -dihydroxy- γ -lactams and functionalized γ -lactams with potential interest for synthetic and bioorganic chemistry.

Introduction

The lactam is a structural motif that is present in a wide variety of bioactive natural compounds and synthetic molecules.^[1] Specifically, functionalized γ -lactams are found in numerous biologically active compounds and several drug molecules, such as the anticonvulsant levetiracetam, the respiratory stimulant doxapram, and the antidiabetic agent glimepiride (Figure 1).^[2]

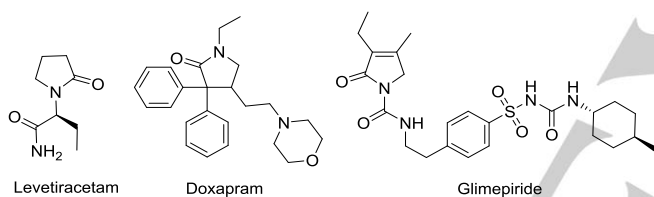


Figure 1. Examples of γ -lactams containing drugs.

Besides recently reported methods for the synthesis of functionalized lactams,^[3] the addition of nucleophiles, such as allylsilanes, isonitriles, alkyl-, and aryl-metals, to *N*-acyliminium ions is one of the most widely used approaches.^[4] Organoboronic acids or esters, which are readily available and stable toward air and water have been extensively used in syntheses of functionalized amines and *N*-heterocycles.^[5] The nucleophilic addition of organoboronic acids and esters to *N*-acyliminium ions, which were derived from 3-hydroxypyrrolidines, was first reported by Batey and co-workers in 1999.^[6] Morgan and co-workers then reported the addition of electron-rich boronic acids to *N*-acyliminium ions to synthesize substituted 4-hydroxypyrrolidin-2-ones and 5-hydroxypiperidin-2-ones.^[7] Recently, Mizuta and co-workers have reported a Petasis-like reaction (PLR) for the synthesis of functionalized piperidines using hydroxypiperidines as the *N*-acyliminium precursors.^[8] Besides these scattered examples of reactions between *N*-acyliminium precursors and electron-rich boronic

acids or esters, a systematic study of the addition of boronic acids to various *N*-acyliminium ions has not yet been reported. Although dihydroxylactams are useful *N*-acyliminium ion precursors, only few synthetic examples, such as the reduction from the corresponding glutarimide or succinimide,^[9] have been reported.^[7, 10]

Herein, a novel versatile approach to *N*-substituted β,γ -dihydroxy- γ -lactams through reductive cyclization and a Petasis-like reaction to functionalized γ -lactams through nucleophilic addition of boronic acids to *N*-acyliminium ions are disclosed.

Results and Discussion

The acetal protected amides **1a-i** were synthesized through the formation of a mixed anhydride using isobutyl chloroformate starting from L-malic acid.^[11] *N*-substituted β,γ -dihydroxy- γ -lactams **2a-h** were then obtained by a novel cyclization strategy through reduction of the dioxolanone carbonyl group of **1a-h** using LiAlH_4 in good to excellent yields. *N*-Pyridin-4-ylmethyl compound **2i** was isolated in low yield due to its high aqueous solubility (Figure 2). The compounds in Figure 2 were obtained as mixtures of diastereoisomers.

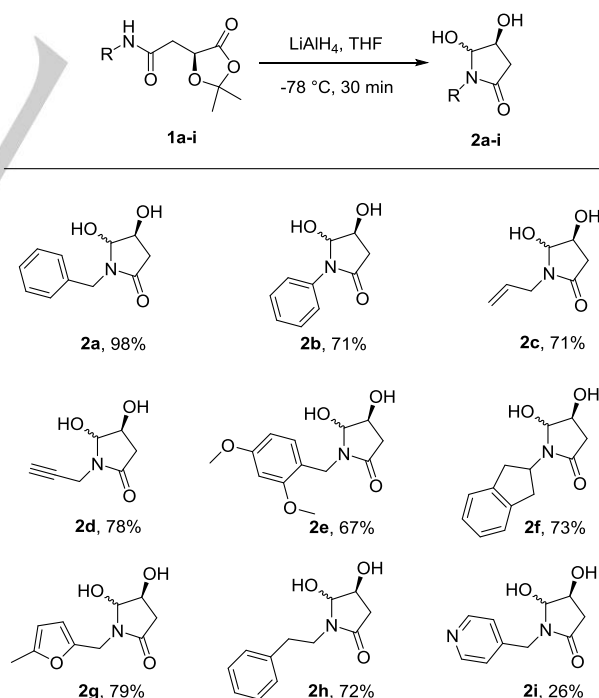


Figure 2. Synthesis of lactams **2a-i** through reductive cyclization.

Using *N*-benzyl-4,5-dihydroxylactam **2a** as the *N*-acyliminium ion precursor, initial experiments were performed under the Batey condition employing methylene chloride as the solvent in the presence

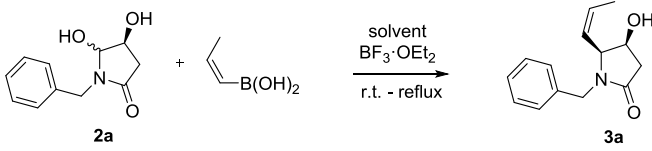
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of boron trifluoride etherate.^[6] The reaction of **2a** with *cis*-1-propen-1-ylboronic acid, phenylboronic acid, and 4-bromophenylboronic acid gave only traces of the expected product after refluxing for 3 days. 2-Furyl boronic acid, which has been successfully applied for various Petasis reactions,^[7] gave the expected product in high yield but with poor diastereoselectivity.

Table 1. Optimization of conditions for the Petasis-like reaction.



Entry	Solvent	Time	Conversion of 2a , % ^[a]	Formation of 3a , % ^[a]
1 ^[b]	CH ₂ Cl ₂	12 h	0	0
2 ^[b]	HFIP	1 h	0	0
3	CH ₂ Cl ₂	12 h	66	trace
4	HFIP	1 h	94	67
5	HFIP	5 h	100	67
6	methanol	1 h	100	0
7	2-propanol	1 h	100	0
8	methanol:HFIP (1:1)	1 h	100	0
9	THF	12 h	69	trace
10	acetone	12 h	73	11
11	acetonitrile	5 h	100	44
12	nitromethane	5 h	100	60 ^[c]
13	1,4-dioxane	12 h	97	trace
14	CH ₂ Cl ₂ :HFIP (1:1)	12 h	100	53

[a] Determined by LC-MS. [b] Absence of BF₃·OEt₂. [c] Both *cis*- and *trans*-isomers were detected on LC-MS with a dr ratio of 2:3.

Based on the initial results and our previous experience with Petasis reactions,^[5b, 12] optimization focused on solvent selection for the reaction between dihydroxylactam **2a** and *cis*-1-propen-1-ylboronic acid (Table 1). First of all, in the absence of BF₃·OEt₂ (entries 1 and 2), no conversion of the starting dihydroxylactam **2a** was observed, indicating that a Lewis acid is indeed necessary for the formation of the *N*-acyliminium ion. Trace of the expected product **3a** was detected after refluxing in methylene chloride for 12 h (entry 3), while changing the solvent to 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) sped up the reaction significantly (entries 4 and 5). The use of other protic solvent systems (entries 6–8) gave full conversion of **2a**, but unfortunately, none of the expected product was observed. A selection of other polar solvents were then tested (entries 9 to 13), where nitromethane gave

the best formation of **3a** as judged from LC-MS, while the diastereoselectivity was poor. A mixture of CH₂Cl₂/HFIP (1:1, v:v) as solvent gave good conversion after 12 h (entry 14), but the formation of **3a** was lower than that in HFIP. Thus, HFIP in the presence of BF₃·OEt₂ was chosen as the most efficient reaction condition for further experiments.

A selection of boronic acids was tested for the PLR under the optimized condition. The results are summarized in Table 2. Similar to the reaction of **2a** with *cis*-1-propen-1-ylboronic acid, which gave only the *cis*-adduct **3a** (entry 1), reactions of **2a** with *trans*-2-chloromethylvinylboronic acid and vinyl boronic acid dibutyl ester gave only the corresponding *cis*-adducts **3b** and **3c** (entries 2 and 3). Phenylboronic acid and 4-bromophenylboronic acid, also yielded the corresponding *cis*-adducts **3d** and **3e** with excellent diastereoselectivity when reacted with **2a** (entries 4 and 5). The good *cis*-diastereoselectivity associated with the above results were lost when electron-rich 3,4-dimethoxyphenylboronic acid and 2,4-dimethoxyphenylboronic acid were used (entries 6–7). An expanded scope of the PLR was then investigated by using aromatic/heteroaromatic β,γ-dihydroxy-γ-lactams **2b**, **2e–h** and aliphatic dihydroxy-γ-lactams **2c–d**. *N*-Allyl-4,5-dihydroxylactam **2c** and *N*-propargyl-4,5-dihydroxylactam **2d** were reacted with *trans*-2-chloromethylvinylboronic acid to selectively afford the expected *cis*-products **3h** and **3i**, respectively (entries 8 and 9), so did the use of vinyl boronic acid dibutyl ester (entry 10). The use of 3- and 2-benzothiénylboronic acids led to both isomers with a favored formation of the *cis*-products (entries 11–12). Reaction between *N*-(2,4-dimethoxybenzyl)-4,5-dihydroxylactam **2e** and thienyl-2-boronic acid did not proceed cleanly and only the major *cis*-isomer **3m** could be isolated in a low yield (entry 13), a compound formed through the intramolecular Friedel-Crafts alkylation was among byproducts detected by LC-MS. The reaction of *N*-(2-dihydroindene)-4,5-dihydroxylactam **2f** with furan-2-boronic acid was fast and similar to the result of using other electron-rich boronic acids, poor diastereoselectivity was observed with formation of the *cis*-product **3n** being favored (entry 14). Reaction of *N*-(5-methylfuran-2-yl)methyl-4,5-dihydroxylactam **2g** with either 4-bromophenylboronic acid or benzofuran-2-boronic acid was unsuccessful and the best result was obtained with the reactive furan-2-boronic acid, albeit affording both isomers in a low yield (entry 15). Poor diastereoselectivity was also observed for the reaction between *N*-phenethyl-4,5-dihydroxylactam **2h** and benzofuran-2-boronic acid (entry 16).

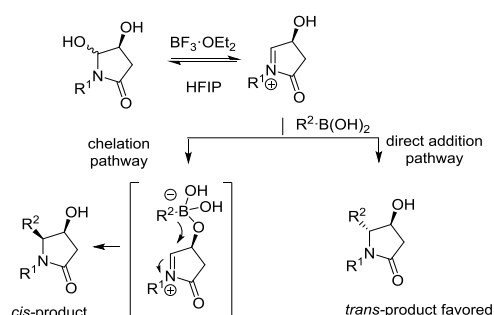
Based on the above results, it was clearly demonstrated that under the optimal reaction condition of using HFIP as the solvent together with of BF₃·OEt₂, high *cis*-diastereoselectivity was achieved by using less reactive boronic acids. In contrast, the use of electron-rich boronic acids significantly shortened the reaction time and gave products of poor diastereomeric purity. Thus, it was proposed that the *N*-acyliminium ion, derived from the corresponding β,γ-dihydroxy-γ-lactam through BF₃ coordination in the presence of HFIP, could follow two reaction pathways with boronic acids: 1) a pathway of direct nucleophilic addition of electron-rich boronic ligand to the electrophilic 5-position of the *N*-acyliminium ion to give both isomers with favored formation of the *trans*-products; 2) a slow chelation pathway that involved Petasis-like nucleophilic addition of boronic acids that were activated through the formation of an initial boronate intermediate, followed by the intramolecular addition of R² to the same

face of the iminium ion intermediate, leading exclusively to the corresponding *cis*-product. Electron-deficient boronic acids, such as 4-bromophenyl and chloromethylvinyl boronic acids, proceeded through the chelation pathway exclusively to give the Petasis-like *cis*-products; more reactive boronic acids, such as 2-furyl and benzothierylboronic acids, reacted with the *N*-acyliminium ion through both pathways to give a mixture of *cis*- and *trans*-isomers (Scheme 1).

Table 2. Petasis-like reactions between γ -lactam **2a-h** and boronic acids.

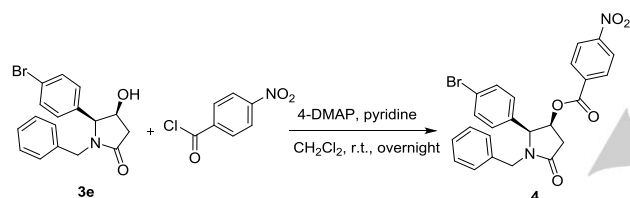
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Entry	Boronic acid/ester	Time	Product ^[a]	Yield, % ^[b] (dr) ^[c]
1		5 h		31 (>20:1)
2		4 d		46 (>20:1)
3		12 h		50 (>20:1)
4		4 d		13 (>20:1)
5		7 d		23 (>20:1)
6		1 h		72 (1:1)
7		0.5 h		48 (1:1)
8		1 d		17 (>20:1)
9		7 d		17 (>20:1)
10		12 h		50 (>20:1)
11		12 h		39 (3:2)
12		1 h		90 (3:2)
13		1 h		11 ^[d] (7:3)
14		0.5 h ^[e]		72 (3:2)
15		1 h ^[e]		20 (3:2)
16		1 h		56 (3:2)

[a] Major diastereoisomer shown. [b] Isolated yields of both isomers after column chromatography. [c] Crude mixture, determined by LC-MS, *cis:trans*. [d] Isolated yield of the *cis*-isomer only. [e] Performed at room temperature.



Scheme 1. Proposed mechanism.

Besides, comparing the results using 3,4-dimethoxyphenyl and 2,4-dimethoxyphenyl boronic acids (entries 6 and 7, Table 2) revealed that steric hindrance had a significant impact on the yield of the reaction.



Scheme 2. Preparation of compound 4.

The stereochemistry of the compounds discussed in this study was assigned based on the magnitude of the vicinal J -coupling constant between the 4- and 5-protons: $J_{4,5}$ around 6 Hz for 4,5-*cis*-stereochemistry and $J_{4,5}$ value ranging from 0 to 3 Hz for 4,5-*trans*-stereochemistry.^[13] To confirm the assignment, compound **3e** bearing a 4-bromophenyl group was reacted with 4-nitrobenzoyl chloride to form the nitrobenzoate **4** for X-ray crystallographic analysis (Scheme 2). The 4,5-*cis*-stereochemistry of **4** was confirmed by inspection of the crystal structure (Figure 3).

Conclusions

A highly efficient reductive cyclization strategy for the synthesis of *N*-substituted β,γ -dihydroxy- γ -lactams starting from L-malic acid has been developed. A wide range of novel *N*-substituted β,γ -dihydroxy- γ -lactams were convenient substrates for Petasis-like reactions with boronic acids promoted by boron trifluoride etherate. Under optimized conditions in HFIP, both electron-rich and electron-deficient boronic acids were successfully employed for the nucleophilic additions to cyclic *N*-acyliminium ions derived from β,γ -dihydroxy- γ -lactams. *cis*-Diastereoselectivity was observed in the Petasis-like reactions when using electron-deficient boronic acids, while electron-rich boronic acids resulted in no or poor selectivity, a phenomenon that we explain by chelation controlled addition and direct addition of boronic acids to

N-acyliminium ions, respectively. A series of functionalized γ -lactams were successfully synthesized employing this method.

Supporting Information (see footnote on the first page of this article): General methods; all experimental procedures and characterization data; copies of the ^1H NMR, ^{13}C NMR, RP-HPLC and/or LC-MS spectra, Dept135 and 2D NMR spectra whenever applicable, for all new compounds. CCDC-1033851 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

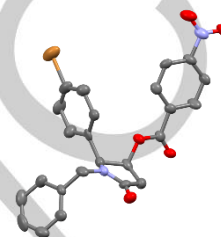


Figure 3. Crystal structure of compound 4.

Acknowledgements

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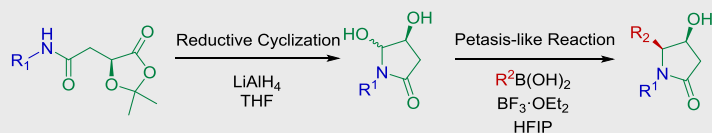
Keywords: Reductive cyclization • Petasis-like reaction • Lactams • Nucleophilic addition • Synthetic methods

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Entry for the Table of Contents

SHORT COMMUNICATION



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and Thomas E. Nielsen*

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A novel approach to N -substituted β,γ -dihydroxy- γ -lactams through reductive cyclization and a Lewis acid mediated Petasis-like reaction to functionalized γ -lactams through nucleophilic addition of both electron-rich and electron-deficient boronic acids to N -acyliminium ions are disclosed.